PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K	A2	(11) International Publication Number: WO 99/36030
		(43) International Publication Date: 22 July 1999 (22.07.99)

(21) International Application Number: PCT/US99/01207

(22) International Filing Date: 19 January 1999 (19.01.99)

(30) Priority Data:
09/007,964 16 January 1998 (16.01.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/007,964 (CON)
Filed on 16 January 1998 (16.01.98)

(71) Applicants *(for all designated States except US)*: DAVITZ, Michael, A. [US/US]; 14 Manor Drive, Goldens Bridge, NY 10526 (US). LEASON, David [US/US]; 176 East 77th Street, New York, NY 10021 (US).

(71)(72) Applicant and Inventor: FOITL, Daniel [US/US]; 600 Harbor Boulevard, Weehawken, NJ 07087 (US).

(74) Agents: LEASON, David et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022–7513 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING DI–HYDROXYTESTOSTERONE DEPENDENT CONDITIONS

(57) Abstract

A pharmaceutical composition for treating DHT dependent conditions including androgenic alopecia is disclosed. An oral dosage form according to the invention includes a therapeutically effective amount of a 5α–Reductase inhibitor and another active compound which binds with androgenic receptors. In a preferred form, the bio–available concentration of the compound which binds with androgenic receptors is limited or controlled to avoid appreciable anti–androgenic side effects, for example, by providing a controlled (timed or sustained release) coating on that active compound. Spironolactone is a particularly preferred compound which binds with androgenic receptors. A preferred dosage form has the ratio of the 5α–Reductase inhibitor to spironolactone in the range of 1:5 to 1:2500. A method for creating an oral dosage form for treating DHT dependent conditions is also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING DI-HYDROXYTESTOSTERONE DEPENDENT CONDITIONS

This application is a continuation-in-part of U.S. Application Serial No. 09/007,964, filed January 16, 1998, for "Pharmaceutical Composition And Method For Treating Di-hydroxytestosterone Dependent Conditions, now pending.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition and the treatment of be di-hydroxytestosterone (DHT) dependent conditions and, more particularly, to a composition and method suitable for treating androgenic alopecia.

BACKGROUND OF THE INVENTION

According to the patent literature, certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, androgenic alopecia which includes female and male pattern baldness, prostatic carcinoma, benign prostatic hyperplasia, and polycystic ovary syndrome are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. See U.S. Patent No. 5,547,957. Whether or not there is an excess

of testosterone, however, the aforementioned undesirable physiological manifestations are all attributable to metabolites of testosterone, and, in particular, to the metabolite di-hydroxytestosterone.

Androgens are intimately involved in male pattern baldness. The active androgen in the balding scalp has been established to be di-hydroxytestosterone (also referred to in the art as di-hydrotestosterone), commonly abbreviated as "DHT." DHT is a metabolite of testosterone resulting from the metabolic activity of the 5α-Reductase enzyme, sometimes referred to as 5α-dihydroxytestosterone or testosterone-5α-Reductase. (Stryer, Biochemistry, W.H. Freeman and Company, San Francisco 1981). Biopsies and biochemical analyses indicate that there are elevated 5α-Reductase levels in males lacking hair.

Two isoenzymes of 5α-Reductase have been identified in human tissue. Type 1 isoenzyme is found in scalp skin, whereas type 2 5α-Reductase is the predominant form in the prostate and, importantly, is associated with hair follicles. (Jenkins et al., J.Clin.Invest., 89:293-300, 1992; Ebling et al., Clin.Endocrin.Metab., 15:319-39, 1986). 5α-Reductase is the principal mediator of androgenic activity in some target organs, e.g. the prostate. DHT is formed locally in the target organ by the action of 5α-Reductase. Inhibitors of 5α-Reductase serve to prevent or lessen symptoms of, among other things, hyperandrogenic stimulation in these organs. See U.S. Pat. No. 4,377,584.

Finasteride is a known inhibitor of human 5α-Reductase; however, it is not known to have any anti-androgenic activity itself. (Storner, J.Steroid Biochem.Mol.Biol., 37, 375-378, 1990). Consequently, the circulating levels of testosterone are not generally believed to be affected. Finasteride is manufactured and marketed by Merck & Co. under the trade name Proscar® and is known to be useful in the treatment of hyperandrogenic conditions when administered in therapeutically effective amounts. See U.S. Pat. No. 4,377,584. The synthesis of finasteride is described in U.S. Pat. No. 4,760,071. Proscar® is a form I polymorph crystal; a form II polymorph crystal of finasteride is also known. See U.S. Pat. No. 5,547,957. A further synthesis of finasteride is described in Synthetic Communications, 30 (17), p. 2683-2690 (1990). Finasteride has been shown to be

effective in the treatment of benign prostatic hyperplasia (BPH), thought to be a DHT dependent condition (see Gormley et al., N.Engl.J.Med., 327:1185-1191, 1992), and, more recently, its utility in the treatment of hair loss has been promoted. At the therapeutic dose of 5 mg/day, finasteride lowers serum DHT levels in men by 65-80% as compared to baseline levels and decreases intra-prostatic levels of DHT by 85% as compared to placebo. (Gormley et al., N.Engl.J.Med., 327:1185-1191, 1992). Proscar® has been approved for use in treatment of BPH since 1994.

The disclosure in the following patent documents are generally pertinent to the treatment of androgenic alopecia and prostatic carcinoma using finasteride, and are hereby incorporated by reference as if set forth in their entireties herein: U.S. Pat. No. 4,377,584, issued Mar. 22, 1983; U.S. Pat. No. 4,760,071, issued Jul. 26, 1988; U.S. Pat. No. 5,547,957, issued Aug. 20 1996; U.S. Pat. No. 5,760,046, issued Jun. 2, 1998; U.S. Pat. No. 5,407,944, issued Apr. 18, 1995; EP 0 285,382, published 5 Oct. 1988; EP 0 285 383, published 5 Oct. 1988; Canadian Patent No. 1,302,277; and Canadian Patent No. 1,302,276. The specific dosages of finasteride exemplified and expressly disclosed in the above-noted disclosures varies from 0.1 to 2000 mg per patient per day.

Another potent inhibitor of human 5α-Reductase is a compound known as dutasteride or GI198745, available from Glaxo Wellcome, Inc. Dutasteride is a dual inhibitor of human 5α-Reductase, that is, it blocks both type I and type II isoenzymes of 5α-Reductase. Dutasteride is presently in phase II/III clinical trials in the United States. Like finasteride, it is a hormone treatment which serves to reduce the amount of dihydrotestosterone circulating in the blood. Because dutasteride blocks both isoenzymes of 5α-Reductase, it can be used in the treatment of androgenic alopecia and also acne vulgaris.

Spironolactone has long been known for its therapeutic qualities as a diuretic and as an anti-androgen. Administration of spironolactone has largely been limited to the female population due to undesirable feminizing side effects in males, such as gynecomastia and impotence. Typically, when spironolactone has been prescribed, it has been administered in doses of approximately 100 mg/day. In females, up to 300

mg/day have been prescribed expressly for the purpose of stopping hair growth at specific sites including the face and chest areas. Therapeutic effects have not been attributed to doses of less than approximately 25 mg/day. By itself, the use of spironolactone has not been associated with clinically effective reversal of alopecia, even at high doses. For men at higher doses, spironolactone would be associated with anti-androgenic side affects making it an undesirable choice of drug. Controlled release of orally administered spironolactone has not been indicated or used in any treatment.

A need remains in the art for an improved composition and method for treatment of DHT dependent conditions, and, for a composition and method particularly suited to the treatment of androgenic alopecia.

SUMMARY OF THE INVENTION

Contrary to popular belief, baldness is reversible. Baldness is a manifestation of a particular type of DHT dependent condition, and is one particular ailment to which the present invention is directed.

More specifically, this invention concerns pharmaceutical compositions for treating and/or reversing certain conditions resulting from the breakdown of naturally produced testosterone. These conditions include androgenic alopecia (also known as "male pattern baldness" or MPB), benign prostatic hyperplasia, acne vulgaris, seborrhea, female hirsutism, prostatic carcinoma, benign prostatic hyperplasia, polycystic ovary syndrome, and other DHT enzymatic dependent disorders. The breakdown product of concern is di-hydroxytestosterone ("DHT"), sometimes referred to as 5α-dihydroxytestosterone or testosterone-5α-dihydroxytestosterone. This invention also concerns a method for treating DHT dependent conditions.

According to one aspect of the invention, a pharmaceutical composition for treating DHT dependent conditions is provided in a dosage form which includes at least two pharmaceutically active compounds. A therapeutically effective amount of finasteride, dutasteride, or other 5α-Reductase inhibitor, for example, a type 2 5α-Reductase isoenzyme, and some spironolactone or spironolactone analog are combined in

the dosage form. The dosage form has a concentration of spironolactone (or analog) selected so as to avoid appreciable anti-androgenic side effects and/or has a coating to control its release and bio-available concentration to less than about 25mg per day. A clinically effective amount of finasteride, if selected for use, is at least about 0.01 mg, and preferably is in the range of about 1 to about 5 mg. A preferred dosage form has the ratio of finasteride to spironolactone in the range of 1:5 to 1:2500.

According to another aspect of the invention, a pharmaceutical composition for treating DHT dependent conditions is provided in a dosage form which includes a 5α-Reductase inhibitor such as finasteride or dutasteride on the one hand and spironolactone or spironolactone analog on the other, wherein the spironolactone (or analog) is provided in an amount which is about 5 to about 2500 times that of the 5α-Reductase inhibitor.

According to a further aspect of the invention, an oral dosage form of the pharmaceutical composition for treating DHT dependent conditions is provided as a gelatin capsule which contains the two active compounds (spironolactone or its analog and a 5α-Reductase inhibitor, e.g., finasteride or dutasteride). As both finasteride and spironolactone are compressible, either or both or another active compound (e.g., dutasteride) may be contained with the gelatin capsule as a powder, granule, microtablet, extruded pellet, or as a coating on a bio-inactive core.

In accordance with another aspect of the invention, the oral dosage form of the pharmaceutical composition for treating DHT dependent conditions is provided as a single, solid dosage form. Finasteride and spironolactone are readily compressible materials and are pressable together into tablets, for example, or extrudable into pellets. Preferably, excipients and binders are included in the material mixture so that more uniform and/or generally non-friable solid dosage forms are produced.

In another aspect of the invention, a method for creating a dosage form suitable for treating DHT dependent conditions of a patient is provided. The method includes the steps of providing either a sustained-release or time-release coating on a second active compound which binds with an androgenic receptor and combining into a single vehicle suitable for oral administration the second active compound with a

therapeutically effective dose of a 5α-Reductase inhibitor. In a preferred form, the daily, bio-available concentration of the second active compound is limited or controlled to release into the plasma of the patient a daily concentration which is insufficient to cause appreciable or observable anti-androgenic side effects. The 5α-Reductase inhibitor is preferably finasteride and the second active component is preferably spironolactone. Dutasteride potentially is a highly preferred compound for use as the 5α-Reductase inhibitor in the pharmaceutical composition of the present invention.

When the oral dosage form is a gelatin capsule containing finasteride as the 5α-Reductase inhibitor, the dosage form can be more safely handled than providing finasteride in an uncoated tablet form. The gelatin capsule provides a convenient vehicle for combining a 5α-Reductase inhibitor such as finasteride or dutasteride with the second active compound which binds with an androgenic receptor, such as spironolactone.

Yet another aspect of the invention concerns a method for treating DHT dependent conditions. The method includes the steps of administering a therapeutically effective dose of a 5α-Reductase inhibitor such as finasteride or dutasteride and administering spironolactone or its analog in a concentration of less than about 25 mg per day. The a 5α-Reductase inhibitor and spironolactone/spironolactone-analog are preferably in an oral dosage form. A further aspect of the inventive method includes administering finasteride as the 5α-Reductase inhibitor in a concentration of at least about 0.01 mg, and preferably is in the range of about 1 to about 5 mg.

The pharmaceutical composition of my invention for treating DHT-dependent conditions can be administered in a wide variety of therapeutic dosage forms, using conventional vehicles, in a single daily dose, or the total daily dosage may be administered in divided doses of two or more times daily. A highly preferred mode is to administer the selected agents using a single vehicle for oral administration such as a tablet or capsule.

Oral dosage forms for the pharmaceutical composition of my invention include scored or unscored tablets, capsules, pills, powders, granules, elixirs, tinctures,

solutions, suspensions, syrups and emulsions. Scored tablets better permit a patient to alter a dosage to suit his or her daily needs.

Tablets can be prepared by mixing the active ingredients of the pharmaceutical composition of my invention with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. Binders, lubricants, disintegrating agents and coloring agents can be incorporated into the mixture if necessary or desired. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Suitable disintegrating agents include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Capsules can be prepared by mixing the active ingredients of the pharmaceutical composition of my invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule.

Liquid forms of the pharmaceutical composition of my invention can be provided in suitably flavored suspending or dispersing agents such as the synthetic and natural gums including, but not limited to, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents which can be employed include glycerin and the like.

The active ingredients of the pharmaceutical composition according to my invention can also be employed in pharmaceutically-acceptable forms such as esters, salts, or as pro-drugs.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 illustrates sites of 5α-Reductase activity in an adult male.

DETAILED DESCRIPTION OF THE INVENTION

The human body is made of many cells. An adult human has approximately one hundred trillion cells (1×10^{13}). Testosterone is present in the plasma and is available to all cells. DHT is a breakdown product of testosterone, and is preferentially concentrated at the conversion sites, that is, the sites having 5α-Reductase activity. Those sites are illustrated in Figure 1. As shown, there are two types of 5α-Reductase: Types I and II. 5α-Reductase of either type is referred to herein more generally as 5α-Reductase.

5α-Reductase is an enzyme which converts testosterone to di-hydroxytestosterone (DHT). DHT is known to be the active androgen in the balding scalp. (Ebling, Clin.Endocrin.Metab., 15:319-39, 1986). High concentrations of DHT have been associated with, among other things, androgenic alopecia. For example, the concentration of DHT in a balding area of the scalp is typically four times that of a non-balding area of the scalp, such as the occipital area of the scalp. (Bingham et al., J.Endocrinol. 57:111-21, 1973). A person with baldness, therefore, is expected to have a "high" concentration of DHT.

5α-Reductase inhibitors operate to reduce the overall conversion of testosterone to DHT when administered in therapeutically or clinically effective doses. Finasteride is a potent inhibitor of 5α-Reductase, and, as such, reduces the overall conversion of testosterone to DHT when administered in a concentration of as little as 0.01 mg/day, and certainly when administered in concentrations of 1 mg or more per day. Presently, finasteride is believed to preferentially inhibit the Type II isoenzyme of 5α-Reductase. Finasteride has been shown to be effective in the treatment of androgenic alopecia. (Diabi et al., J. Clin. Endocrinol. Metab., 74:345-350, 1992). Finasteride is commercially available under the brand names Proscar® (a 5 mg oral dosage tablet form) and Propecia® (also an oral dosage form, in 1 mg tablets) of Merck & Co. Studies have shown finasteride to be effective in doses as low as 0.01 mg/day to reduce DHT levels in scalp, skin and plasma. In other words, finasteride, taken alone --to an extent--, has reduced alopecia and enabled regrowth of some hair in the balding area. Results are

generally observable after three to six months of taking finasteride; however, for some people, finasteride is ineffective and does not stem or reverse hair loss.

As a consequence of natural genetic variation, each individual has a different number of DHT receptor sites on hair follicles. Depending on the normal DHT concentration level in the plasma and the number of DHT receptor sites that a given individual has, the likelihood of that individual experiencing alopecia will vary. Specifically, individuals having a large number of DHT receptor sites and a high DHT plasma level are more likely to experience androgenic alopecia than an individual having fewer DHT receptor sites and/or a lower DHT plasma concentration. By reducing the overall conversion of testosterone to DHT, finasteride serves as one particularly suitable agent for reducing overall DHT plasma levels. This reduction in DHT level increases the individual's chances of reversing alopecia. Nevertheless, for those individuals having multiple DHT receptor sites, the reduction in DHT plasma level due to finasteride (or another 5α-Reductase inhibitor) alone is ineffective or not sufficiently effective to reverse alopecia. This clinical result is observed notwithstanding the fact that finasteride is known to reduce DHT levels.

In accordance with my invention, I have discovered, surprisingly, improvements in the reversal of androgenic alopecia, a DHT-dependent condition, without appreciable side effects when a controlled dose of spironolactone or its analog is administered on a daily basis together with a 5α-Reductase inhibitor, such as finasteride or dutasteride. When spironolactone is taken in combination with finasteride, for example, a synergistic effect in the patient is achieved. Finasteride reduces the level of DHT by blocking conversion of testosterone by 5α-Reductase. Dutasteride is believed to operate in the same way. It appears that spironolactone potentiates the activity of finasteride and, in theory, any other form of a 5α-Reductase inhibitor, by blocking transduction of the signal after DHT binds to the cell. In theory, a spironolactone analog, that is, an agent that functions in a bio-equivalent way to spironolactone, will also potentiate activity of a 5α-Reductase inhibitor; however, none is known to the inventor at this time. Spironolactone and its analogs are more generally referred to herein as spironolactone. Finasteride and

spironolactone together significantly reduce the biological effect of DHT on the cell; the same is expected for the combination of dutasteride and spironolactone. Clinically, the effect observed is increased hair growth (including density, regrowth and length) in balding areas, at a rapid rate, as compared to the use of finasteride alone.

Spironolactone, and its analogs, act by competing with DHT for a DHT binding site in biological tissues. Spironolactone is an example of a 17-spironolactone steroid, which is a competitive antagonist of adrenal mineralocorticoids, among which aldosterone is the most potent. This action was central to the FDA approved use of this drug as a potassium-sparing mild diuretic. The drug competitively inhibits DHT binding at the androgen receptor and suppresses androgen secretion and/or production from the gonads as well as the adrenal glands. Spironolactone's biological effects occur because it inhibits the target organ response to DHT by competing for the cytosolic DHT receptor. This competitive inhibition interferes with the binding and subsequent translocation of the receptor complex to the nucleus of the cell. Spironolactone is also converted by progesterone 17-hydroxylase to an active metabolite that reversibly inhibits the adrenal and gonadal cytochrome P-450. Spironolactone's anti-androgen effects are complex, the side effects are well known, and the biological mechanism of its action is variable.

Other active compounds instead of or in addition to spironolactone can be used for their anti-androgenic effects, specifically, their ability to bind at the androgenic receptor (that is, the DHT binding site). For example, cyproterone acetate is an antiandrogen associated with strong feminizing side effects when used in conventional therapies of high doses, that is, substantially greater than about 50 mg/day. However, the side effects can be avoided, and the compound instead can be used to bind with androgenic receptors and thereby potentiate the activity of the 5α-Reductase inhibitor, as described above with respect to spironolactone. Also, cimetidine is an H_2 blocker ordinarily administered to prevent stomach acid. Cimetidine is generally considered safe for oral administration and is associated with mild antiandrogenic activity which makes it suitable for binding androgenic receptors and for potentiating the activity of a 5α-Reductase inhibitor such as finasteride.

According to my invention, highly effective treatment of DHT dependent conditions is achieved by administering a 5α-Reductase inhibitor such as finasteride and spironolactone (or its analogs), with the amount of bio-available spironolactone (analogs) being controlled or limited to not more than about 25 mg/day. At this dosage level of spironolactone, there are no appreciable anti-androgenic side affects in a great majority of the population and, surprisingly, the combination of drugs has a profound effect on reversing alopecia. Preferably, finasteride or dutasteride are combined with spironolactone and administered in a single dosage form, such as one of the dosage forms described above in the summary of my invention and most preferably in an oral dosage form. As described above, other active compounds which bind with androgenic receptors can be used in lieu of or in combination with spironolactone or its analogs. What is important to the invention is that the second active compound be introduced into the plasma to compete with androgens for the binding site, such as an androgenic cytoplasmic receptor. Preferably, the binding is competitive and reversible so that any potential side effects are minimized or avoided by controlling the daily dosage or terminating the therapy.

Other active materials can be provided in the dosage form for treating androgenic alopecia and other DHT-dependent conditions, including one or more of the following: a potassium channel opener, a vasodilator, minoxidil, nitroglycerin, diazoxide, estradiol, calcium ion flux inhibitors (i.e., calcium channel blockers), nifedipine, or a pharmaceutically acceptable salt of any of the foregoing. For a further description of particular vasodilators and estradiols that are suitable for treating androgenic alopecia, including a description of appropriate daily dosages and dosage forms, see the aforementioned U.S. Pat. No. 5,407,944, incorporated herein by reference.

Because finasteride need only be administered at a concentration of about 0.01 mg/day, in accordance with one embodiment of my invention, treatment of DHT dependent conditions comprises administering finasteride and spironolactone in a ratio of as much as about 1:2500, with the bio-available concentration of spironolactone being controlled or limited to no more than about 25 mg/day. Other 5α-Reductase inhibitors

such as dutasteride may require greater amounts per day, and spironolactone analogs may be used in different compositions according to my invention and may require somewhat more or less dosage per day, to have an analogous bio-availability to spironolactone.

In a preferred form, one or more of the pharmaceutically active compounds are provided in a dosage form which includes a sustained- or time- release coating to enhance its bio-availability within the plasma. Such coatings are well known in the art. For example, either or both active compounds can be coupled with soluble polymers as targetable drug carriers. Suitable polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Also, the pharmaceutical composition of my invention can be coupled to a biodegradable polymer to achieve controlled release of one or more of the active ingredients, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. The use of such coatings on spironolactone, for example, enables a steady, low dose of spironolactone to be continuously available throughout the day. Such coatings eliminate concentration spikes in bioavailablity of the active ingredient which would otherwise occur if the release of the active ingredient were not controlled or timed. It is within the scope of my invention to provide such coatings on the finasteride or other 5α-Reductase inhibitor and/or on spironolactone, a spironolactone analog or other active compound which binds with androgenic receptors.

In the following examples, I report results of a non-invasive measuring technique in which the progress of my patients was observed and recorded. In each example, the same methodology was performed and the finasteride, spironolactone, or both was taken in an oral dosage form. At a visit prior to commencing therapy, the patients' heads were photographed, including both vertex and anterior hair line views, to establish a base-line reference. In follow-up visits, the patients' hair was inspected (both visual and tactile) and notes were recorded along with progress photos (vertex and anterior

hair line views). I observed hair regrowth, including vellus hairs, in areas of prior alopecia with respect to the base-line reference photographs. I also observed hair density by comparing the degree of visible scalp and the overall thickness of the hair with respect to the base-line reference photographs. Moreover, I noted changes in hair length through visual and tactile inspection and the patient's comments.

Example 1

Patients who took finasteride at doses of 5 mg/day in conjunction with spironolactone doses of 25 mg/day or less over the course of several months were closely evaluated in comparison to patients who took finasteride alone. I observed superior objective and subjective clinical responses in hair regrowth among the treatment group including hair density and length verses the patients in the control group who took finasteride alone at doses of 5 mg/day. No effect on plasma testosterone (free or bound) or prostate specific antigen was noted in either group (finasteride with spironolactone or finasteride alone). Further, no appreciable effect on libido, breast tenderness, erectile function, or muscle mass was noted in either group.

Example 2

Patient A with androgenic alopecia was administered 5 mg/day dose of finasteride (Proscar brand) in combination with 25 mg/day of spironolactone (aldactone brand) as a therapy. After two months, hair density and length increased. At six months, hair density was markedly increased and hair regrowth and length also were increased.

Example 3

Patient A of Example 2 discontinued use of spironolactone after eleven months, having achieved significant reversal of the androgenic alopecia. Patient A continued alopecia therapy using finasteride alone in a daily dosage of 5mg. Four months later, hair density was only moderately improved, and hair regrowth and length only slightly increased. Ten months later, no change in hair regrowth, length, or density was

observed. Previously, when both finasteride and spironolactone were being administered on a daily basis, the same patient experienced significantly greater increase in hair density and greater regrowth and length.

Example 4

Patient B, seeking treatment for androgenic alopecia took finasteride in a 5 mg/day dose (Proscar brand) for six months, and no change in hair density, regrowth or length was observed. The patient was monitored three times during that time period.

Example 5

Patient B from Example 4, with androgenic alopecia, continued the 5 mg/day dose of finasteride therapy (Proscar brand) and, at the six month mark, added 25 mg/day of spironolactone (aldactone brand) for a combined active-drug therapy. Three months later, hair density and regrowth were improved. Two months thereafter, patient B showed a marked increase in hair density and length as well as improved hair regrowth. Eight months after taking finasteride and spironolactone together, a marked further improvement in hair density was observed, as well as continued increase in hair regrowth. Continued improvements in length, regrowth and density were again observed seventeen months after commencing the combined therapy.

Example 6

Patient C, also seeking treatment for androgenic alopecia took finasteride for four months at a daily dosage of 5 mg (Proscar brand). A slight increase in hair density was observed at the fourth month.

Example 7

Patient C from Example 6, continued the 5 mg/day dose of finasteride therapy (Proscar brand) and, after four months, added 25 mg/day of spironolactone (aldactone brand) for a combined active-drug therapy. Over the next five months, hair

density and regrowth showed continued improvement, and hair length increased. By the fifth month, marked improvement in hair density and regrowth were observed, as well as increased hair length.

Example 8

Several patients under my care, seeking treatment for androgenic alopecia, took finasteride in a 5 mg/day dose (Proscar brand) for between eleven and fifteen months and had no observable change in Hamilton stage. These patients each exhibited an initial Hamilton stage ranging from stage V to stage I.

Example 9

Several patients under my care, seeking treatment for androgenic alopecia, took finasteride in a 5 mg/day dose (Proscar brand) in combination with 25 mg/day of spironolactone (aldactone brand) for between five and ten months had a significant change in Hamilton stage down to stage 0, reversal of alopecia. These patients each exhibited a different initial Hamilton stage ranging from stage IV to stage II/I.

While the combination of a 5α-Reductase inhibitor with spironolactone in a concentration of 25 mg/day or less is preferred, enhanced growth can be achieved in some patients (human or other mammal) by increasing the daily dosage of spironolactone. However, increases in spironolactone to a concentration level of about 50 mg/day or more has been found to increase the risk of feminizing side effects in some patients. Using controlled or timed release of spironolactone or other active compounds which bind with androgenic receptors, however, permits greater amounts of such active compounds to be used with a concomitant lessened risk of feminizing side effects. The appropriate dosage level above 25 to 50 mg/day can be determined on a case-by-case basis.

The 5α-Reductase inhibitor used in the composition of this invention for treating DHT dependent conditions preferably is a type 2 inhibitor. The 5α-Reductase 2 inhibitor, if selected for use in the composition to be administered, may have the structural

formula I or II or a pharmaceutically acceptable salt thereof, as disclosed in U.S. Pat. No. 5,547,957, representative and corresponding compounds of which are also disclosed therein.

The pharmaceutical composition and method of my invention can be used in any patient (human or other mammal) seeking to reduce or stem ailments associated with DHT dependent conditions, such as those seeking to induce, maintain or increase hair growth.

The term "treating DHT dependent conditions" is intended to include the reducing, arresting and/or reversing of the following ailments: androgenic alopecia, which includes female and male pattern baldness, acne vulgaris, seborrhea, female hirsutism, androgenic alopecia, prostatic carcinoma, benign prostatic hyperplasia, and polycystic ovary syndrome, and other DHT dependent conditions now known or later discovered.

The dosage regimen utilizing the pharmaceutical composition of my invention is selected in accordance with a variety of factors including species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. A physician (or veterinarian) of ordinary skill can readily determine and prescribe the lowest effective dose required to treat the DHT dependent condition. In particular, the amount of either active compound (namely, a spironolactone, spironolactone analog or other active compound which binds with androgenic receptors on the one hand, and/or the finasteride or other 5α-Reductase inhibitor on the other) can be reduced from an acceptable starting concentration until a determination is made as to the daily bio-available concentration required to (1) achieve a clinically observable increase in hair growth, (2) maintain a desired state, or (3) achieve a desired change in another DHT-dependent condition is determined.

Having thus described certain preferred compositions of the present invention, it is to be understood that the above described pharmaceutical composition and methods are merely illustrative of the principles of the present invention, and that other compositions and methods may be devised by those skilled in the art without departing from the spirit and scope of the invention as claimed below.

What is claimed is:

1. A composition for treating DHT dependent conditions of a patient, comprising:

an oral dosage form having pharmaceutically active compounds consisting of an amount of a 5α-Reductase inhibitor which is effective for treating DHT dependent conditions and a second active compound which binds with an androgenic receptor, wherein the second active compound is coated to provide one of a sustained-release and time-release.

2. The composition of claim 1, wherein the oral dosage form is selected from the group consisting of: tablets, capsules, pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions.

3. The composition of claim 1, wherein the oral dosage form is a gelatin capsule and wherein at least one of the 5α-Reductase inhibitor and the second active compound in the gelatin capsule is one of a powder, granule, microtablet, extruded pellet, or coating on a core.

4. The composition of claim 1, wherein the coating on the second active compound is one of a soluble polymer and a biodegradable polymer.

5. The composition of claim 4, wherein the second active compound is spironolactone.

6. The composition of claim 5, wherein the spironolactone in the dosage form has a weight of less than about 25 mg.

7. The composition of claim 6, wherein the 5α-Reductase inhibitor is selected from the group of finasteride and dutasteride.

8. The composition of claim 5, wherein the soluble polymer is selected from the group of polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, and polyethyleneoxidepolylysine substituted with palmitoyl residues, and wherein the biodegradable polymer is selected from the group of polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

9. The composition of claim 5, wherein the concentration of bio-available spironolactone in the dosage form is limited or controlled to release into the plasma of the patient a daily concentration in an amount which is insufficient to cause appreciable or observable anti-androgenic side effects.

10. The composition of claim 9, wherein the daily concentration of spironolactone is no more than about 25 mg per day.

11. A composition for treating DHT dependent conditions of a patient including androgenic alopecia, comprising an oral dosage form comprising a 5α-Reductase inhibitor and a spironolactone having a coating, the ratio of the 5α-Reductase inhibitor to spironolactone being about 1:5 to about 1:2500.

12. The composition of claim 11, wherein the 5α-Reductase inhibitor is selected from the group of finasteride and dutasteride.

13. The composition of claim 11, wherein the oral dosage form is a gelatin capsule and wherein the coating on the spironolactone controls the release of spironolactone within the patient, the coating being one of a soluble polymer and a biodegradable polymer.

14. The composition of claim 13, wherein the soluble polymer is selected from the group of polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, and polyethyleneoxidepolylysine substituted with palmitoyl residues, and wherein the biodegradable polymer is selected from the group of polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

15. The composition of claim 14, wherein the 5α-Reductase inhibitor is selected from the group of finasteride and dutasteride.

16. The composition of claim 13, wherein the concentration of bio-available spironolactone in the dosage form is limited or controlled to release into the plasma of the patient a daily concentration which is insufficient to cause appreciable or observable anti-androgenic side effects.

17. The composition of claim 16, wherein the daily concentration of spironolactone is no more than about 25 mg per day.

18. A method for creating an oral dosage form suitable for treating DHT dependent conditions of a patient, comprising the steps of:

providing one of a sustained-release and time-release coating on a second active compound which binds with an androgenic receptor; and

combining into a single vehicle suitable for oral administration the second active compound with a therapeutically effective dose of a 5α-Reductase inhibitor.

19. The method of claim 18, wherein the daily, bio-available concentration of the second active compound is limited or controlled to release into the plasma of the patient a daily concentration which is insufficient to cause observable side effects.

20. The method of claim 19, wherein the second active compound is a spironolactone.

21. The method of claim 20, wherein the daily concentration of spironolactone is no more than about 25 mg per day.

22. The method of claim 20, wherein the 5α-Reductase inhibitor is selected from the group of finasteride and dutasteride.

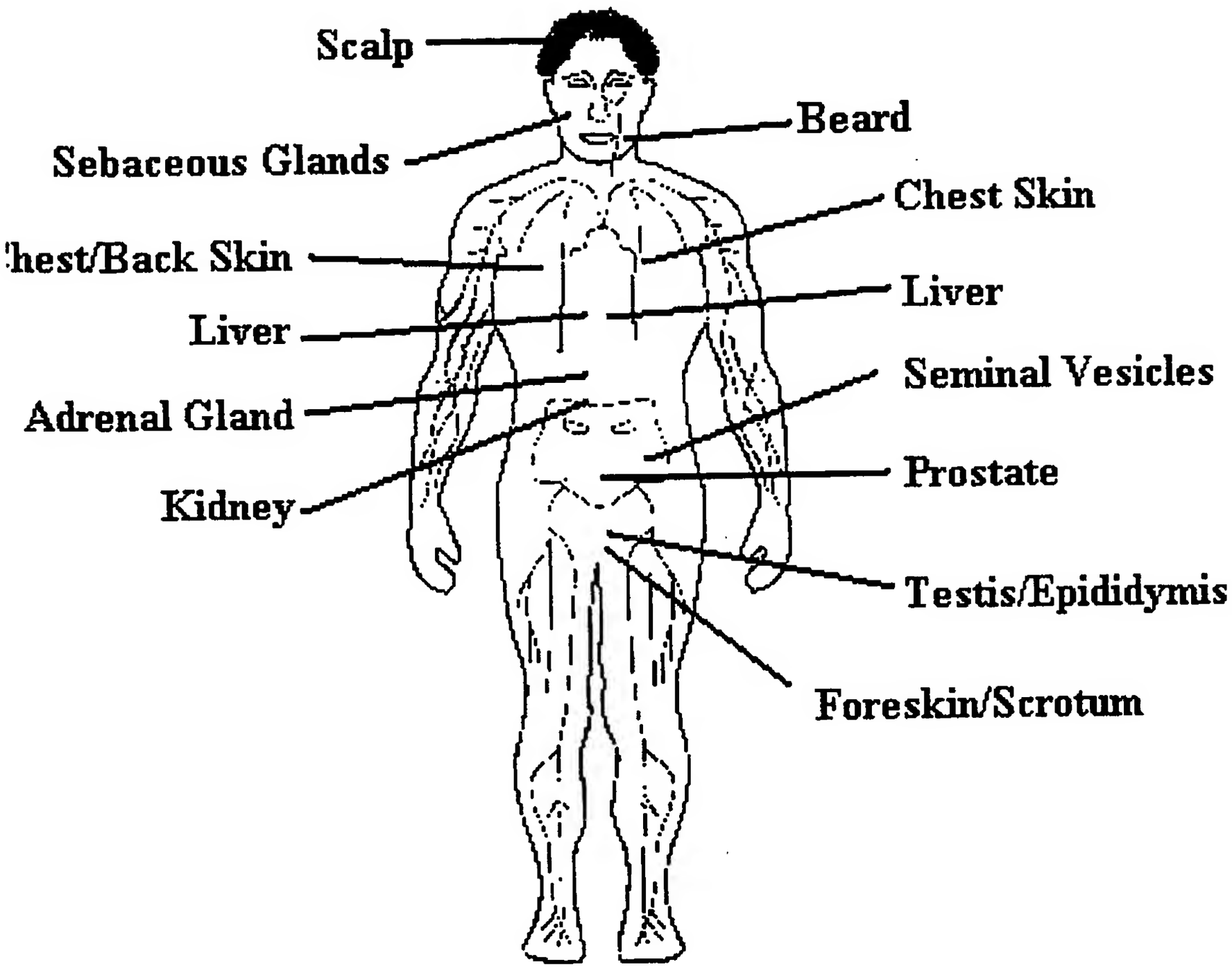
Type I
Type II
Scalp
Beard
Sebaceous Glands
Chest Skin
Chest/Back Skin
Liver
Liver
Seminal Vesicles
Adrenal Gland
Prostate
Kidney
Testis/Epididymis
Foreskin/Scrotum

Fig. 1